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Logical modelling of cellular decision processes with GINsim

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Systems biologists are facing the difficult challenge of modelling and analysing regulatory networks encompassing numerous and diverse components and interactions. Furthermore, available data sets are often qualitative, which complicates the definition of quantitative computational models.

Logical modelling constitutes a flexible framework to build qualitative predictive models, which can be readily analysed or simulated as such, and potentially used as scaffolds to build more quantitative (continuous or stochastic) models. The dynamics of such models can be represented as State Transition Graphs (STG). It is then particularly relevant to identify subgraphs corresponding to dynamical attractors (i.e. terminal strongly connected components in STGs), as well as their reachability properties. For complex networks, however, the explicit construction of state transition graphs can be cumbersome or even intractable. This led us to develop several complementary computational strategies, which are implemented in our logical modelling software suite, GINsim [2, 8].

A first strategy consists in deducing properties directly from the model, defined as a regulatory graph (i.e. a set regulatory components or nodes, connected by signed arcs representing regulatory interactions). Using Multi-valued Decision Diagrams to represent (multi-level) logical updating rules enabled the development of efficient algorithms for the identification of all the stable states of a model, or yet to relate specific (positive or negative) regulatory circuits with specific dynamical properties (e.g., multiple attractors or sustained oscillations) [7, 11]. The rationale consists in deducing the structure of the state transition graph directly from the regulation graph. We are currently working on the identification of complex attractors, using recent mathematical results connecting the presence of positive or negative regulatory circuits in the regulatory graph with the occurrence of multiple attractors or dynamical cycles in the state transition graph.

A second strategy leads to the reduction of state spaces, either by reducing the model (the regulatory graph) or directly by working on the STG. More specifically, GINsim encompasses a reduction method that essentially preserves the dynamical properties of the model, although some reachability properties could be lost [10].

More recently, we have developed an algorithm to compact state transition graphs on the fly. The result of a simulation is compressed into a hierarchical graph, where the nodes represent connected sets of states or components, each symbolically represented by a decision diagram. Each component is labelled as either stable state (terminal nodes in the state transition graphs), cyclic attractor (terminal strongly connected components), transient cycle(s) (non-terminal strongly connected components) or basins of attraction (subsets of transient states), depending on the topology of the underlying transition sub-graph.

Finally, we are currently considering the application of formal methods, in particular model-checking techniques. To that end, GINsim has recently been equipped with an export facility, which enables the use of NuSMV to query logical models [6].

Beside these recent developments, we are developing means for incremental, compositional verification, to analyse large logical models defined as compositions of simpler regulatory modules.

All methodological developments are motivated by and used to tackle the analysis of regulatory networks involved in the control of cell fate, including of cell proliferation, differentiation and programmed death [1, 3, 4, 5, 8, 9, 12, 13]. In this talk, we will refer to ongoing applications to the modelling of MAPK signalling pathways or of the network controlling hematopoietic cell specification in mammals, or yet of the network controlling the specification of mesoderm in drosophila embryo. These applications are described in more details in the contributions of Grieco et al., Collombet et al., Niarakis et al., and Mbodj et al. in these proceedings.

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